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Raymond A Miller
Firm 21269
One Mellon Center
50th Floor 500 Grant Street
Pittsburgh, PA 15219

EXAMINER	
WOLLENBERGER, LOUIS V	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,657	DRUMM ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/2/08, 2/7/08, and 11/16/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,9,10,16,19 and 94-98* is/are pending in the application.

4a) Of the above claim(s) *94,95 and 97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,9,10,16,19,96 and 98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/4/07; 2/4/08; 3/4/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group IV, claim(s) 4-6, 9, 10, 16, 19, 96, and 98, drawn to a method for the treatment of an eye disorder comprising administering a therapeutically effective amount of a dsRNA and detecting a product of the target gene of said dsRNA, in the reply filed on 5/2/08 is acknowledged. The traversal is on the ground(s) that the special technical feature cited by the Examiner is, contrary to the Examiner's assertions, a contribution over the prior art. This is not found persuasive because it is the Office's position that the step of treating a disorder of the eye by administering outside the blood-retinal barrier a dsRNA complementary to a target gene in the eye is taught and/or suggested by the prior art for the reasons set forth in the Action mailed 5/16/07 and the Requirement mailed 4/4/08. Further, methods of preparing dsRNA and diagnosing disorders and predispositions to disorders of the eye involve steps and materials, and thereby special technical features, not present in or required by the elected and originally presented method for treating a disorder of the eye by administering a dsRNA. Applicant further argues there is no burden to search and examine all the claims. However, burden is not consideration for Restriction for lack of unity in a National Stage filing. The Examiner is not bound by the presence or absence of any such finding in a related PCT filing, as each case is treated individually on its own merits.

The requirement is still deemed proper and is therefore made FINAL.

Status

With entry of the amendment to the claims filed 5/2/08, claims 1, 4-6, 9, 10, 16, 19, and 94-98 are pending. Claims 94, 95, and 97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 4-6, 9, 10, 16, 19, 96, and 98 are examined herein.

Applicant's response originally filed on 11/16/07 and again on 2/7/08 in reply to the Non-Final Rejection mailed 5/16/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 5/16/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Domestic and Foreign Priority

The previous finding that the claims were insufficiently supported by the prior filed applications for the reasons stated therein is withdrawn in view of applicant's amendments to the claims, originally filed 11/16/07. Applicant refers to an English language translation of Foreign Priority Application EP 02008761.5; however, no such translation is found in the information file wrapper. If Applicant intends to establish support for the instant claims by pointing to passages therein that specifically provide written description and/or enabling support, Applicant is requested to make an English language translation of said document of record.

However, the lack of support finding remains effective because no support is found in either of the domestic or foreign priority documents, and applicant has not pointed out with particularity where support may be found, for the instant claims as amended on 11/16/07. In

particular written description and/or enabling support is not found in Provisional Application 60/431172 or Foreign Priority Application EP02008761.5 for a method of treating RPE, neurosensory retina, choroid, AMD, or diabetic retinopathy by administration of dsRNAs. Further, no support is found in either of the prior filed applications for dsRNA targeting SEQ ID NO:3, or for methods of treatment further comprising detecting the product of the target gene.

To be entitled to the benefits of 35 U.S.C. 119(e), the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/431,173 and EP 02008761.5 fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for at least instant claims 4–6, 10, 19, and 96.

Thus, for purposes of this examination, the earliest effective filing date of claims 4–6, 10, 19, and 96 is considered to be that of PCT/EP03/04003, filed 4/16/03.

Claim Rejections - 35 USC § 112, first paragraph (written description)

Claims 4 and 6 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

As explained in the Action mailed 5/16/07, while the specification adequately describes the dsRNAs necessary to treat at least one eye disorder associated with the expression of SEQ ID NO:3 or VEGF, the specification does not adequately describe the genus of dsRNAs necessary to treat at least one disorder representative of the group of disorders of the retinal pigment epithelium, neurosensory retina, choroid, and combinations thereof, nor any disorder representative of wet-age macular degeneration or diabetic retinopathy.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

Adequate written description support does not exist in the instant application for all these methods because neither the instant application nor the prior art adequately describe a representative number of target genes correlated with the countless number of eye disorders embraced by the instant claims nor adequately describe the particular features or distinguishing characteristics common to genes that are related to or correlated with the multitude of eye disorders treatable by the instant methods. As a result, Applicants have not described the target genes to be targeted by the instant methods using inhibitory dsRNA. Logically, if neither the instant application nor the prior art enables one of skill in the art to instantly recognize the genes to be targeted by the instant methods, Applicants have not described the genus of dsRNAs

necessary to treat all the disorders embraced by the claims. Therefore, Applicants have not demonstrated they were in possession of the genus of methods now claimed.

Thus, the claims are extremely broad. The claims encompass a large genus of methods requiring a multitude of distinct dsRNA compounds for modulating (inhibiting or upregulating) any gene in any species associated with any disorder of the eye, and in more narrow embodiments, any of the specific classes of disorders recited in claims 5 and 6.

With regard to the target genes and dsRNAs needed to modulate such genes for the treatment of any eye disorder, the Examiner is unable to readily find any disclosure in the instant application or prior art nor any evidence in the case record establishing the correlation between a representative number of target genes and the treatment of the genus of eye disorders, wherein the target gene is of particular relevance to angiogenesis, neovascularization, RPE, choroids, AMD, and diabetic retinopathy in the eye. Such disorders are expected to involve a complex array of genes and genetic factors. While paragraph 59 of the instant application points to a possible genetic element in AMD, the specification fails to identify the gene(s) responsible or provide any guidance as to which genes in particular should be targeted to treat AMD.

As a result, one of skill in the art would be left to de novo trial and error experimentation to identify such genes to practice the instant method. One of skill would therefore not recognize that Applicants were in possession of the genus of methods now claimed at the time of filing.

The dsRNAs required for the methods are recited in terms of their function only, there is no art-recognized correlation between their structure and their required function (treatment of eye disorders), and the specification does not provide the support needed to enable one skilled in the art to predict with a reasonable degree of confidence the structure of the dsRNAs from a

recitation of function alone. What is needed is a description of the target genes that have been clearly correlated with the eye disorders that may be treated by the instantly claimed methods.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations." (Tronzo v. Biomet Inc., 156 F.3d 1154, 1158, 47 USPQ2d 1829, 1832 [Fed. Cir. 1998]).

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

MPEP 2163 states in part that "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within

the genus, one must describe a sufficient variety of species to reflect the variation within the genus. >The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

In the instant case, applicants have not satisfied either of these criteria. That is, the instant application discloses no correlation between the structures of the genus of target genes and the genus of eye disorders. Thus, Applicant has not demonstrated possession of the genus of dsRNAs needed to practice the instant methods.

While the specification and prior art adequately describes one exemplary target gene for the treatment of excessive angiogenesis, VEGF, and one target gene for the treatment of an eye disorder in general, SEQ ID NO:3 (claim 19), evidence is not found clearly establishing a link between any other genes and the disorders now embraced, wherein applicant may clearly envision the structure of the dsRNAs needed to treat that disorder.

Apart from GFP, and the gene targets SEQ ID NO:1, 2, and 3 (see page 18 of specification as originally filed), a review of the specification fails to find any description, by words, structures, figures, diagrams, or formulas, of a representative number of dsRNA species nor any feature common to the genus that may be used in the instant methods to treat any CNS or eye-related disorder. While the specification teaches at pages 52-54 that dsRNA targeting GFP may be delivered to the retina of a transgenic mouse via intravenous injection and that GFP expression in the retina may be reduced by systemic delivery in a mouse, this example is not

directed to the treatment of any eye or CNS disorder and does not describe any dsRNA or siRNA or any vector thereof, nor any other molecule for use in the instant methods to treat an eye or CNS disorder. And while pages 55-58 list several genes, there is no disclosure explaining the relevance of these genes to any particular disorder nor any description of the compounds that are to be used to inhibit or agonize these genes so as to provide a definitive treatment effect. While these genes may indeed be suitable targets for a given disorder, even if one knew which gene was related to any given disorder and whether or not to inhibit or agonize the gene or gene product, one of skill in the art would, nevertheless, be left to de novo screening methods to identify the dsRNAs having the desired activity to produce the desired therapeutic effect.

MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)."

As taught by Weber et al. (previously cited), page 6264, "Mutations in any one of the many genes involved in the complex biochemistry of the eye could theoretically impair vision." Applicants have not described which genes of the many possible are specifically linked to the disorders treatable by the instant methods, which treat disorders by inhibiting the expression of a gene.

Accordingly, only methods comprising the use of dsRNAs targeted to SEQ ID NO:3 and VEGF meet the written description requirement.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Response to Arguments

Applicant's arguments filed have been fully considered but are not persuasive. The specification fails to provide adequate correlation between any particular target gene and at least one disorder of the eye related to any of those recited in claims 5 and 6 such that one of skill would immediately recognize the dsRNAs necessary to treat any such disorder in the manner intended and required by the instant claims. The table at pages 55-58 provides nothing more than a list of genes and their biochemical activities. No physiological or pathophysiological connection is established therein, leading one of skill to select one or more of the gene therein as a target and there is no evidence suggesting that each one is a therapeutically suitable target for each of the disorders defined by the claims.

With regard to Applicant's assertion that the disclosure enables one of skill to deliver the genus of dsRNAs across the blood-retina barrier, the Examiner agrees. However, the instant rejection is not for lack of enablement, but for a description of the dsRNAs needed to practice the inventions of claims 5 and 6, by either describing a representative number of dsRNAs thereof or showing by way of extrinsic or intrinsic evidence that one of skill would have recognized at the

time of filing the at least one target gene that should be targeted by said dsRNA to result in the claimed therapeutic effect. Evidence should be pertinent to the question of possession, wherein one of skill would recognize applicant was in possession of the dsRNAs necessary to treat each of the disorders of claims 5 and 6 because the art or instant specification had established a clear link between inhibition of the target gene or gene product and the disorder.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Until such evidence is found, claims 5 and 6 remain rejected for lack of written description support because one of skill would not have recognized Applicant was in possession of the dsRNAs necessary to practice the full scope of the methods as now claimed.

***

Claims 5, 6 and 19 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the expression of SEQ ID NO:3 and VEGF in the eye, and to a method of treating angiogenesis and/or neovascularization associated with the expression of VEGF, comprising administering a dsRNA outside the blood-retina barrier, does not reasonably provide enablement for methods of treating disorders related to the retinal pigment epithelium, neurosensory retina, choroid, or any combinations thereof, wet age-related macular degeneration, diabetic retinopathy, or any disorder related to the expression of SEQ ID NO:3.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Neither the prior art nor the specification enable one of skill to practice the full scope of the methods now claimed without undue experimentation, because the specification does not teach the genus of genes specifically overexpressed or aberrantly expressed, i.e., as mutant isoforms in the complete genus of eye disorders, and how such expression is specifically related to the eye disorders embraced by and specifically recited in the instant claims. Such information is essential to the practice of the instant methods. While the specification provides enabling disclosure for delivering dsRNA into the eye by administration outside the blood-retina barrier, the specification is not considered to be enabling for treating at least one disorder in each the

categories specified by claims 5 and 6 because the neither the specification nor the prior art has established a nexus linking the inhibition of at least one target gene with each of the disorders. As a result there is inadequate direction and guidance in the specification to enable one of skill to make and use the dsRNAs necessary to treat each of the disorders without engaging in undue experimentation.

With regard to SEQ ID NO:3, while the specification asserts that malfunction of this gene has also been associated with autosomal recessive retinitis pigmentosa, neither the specification nor the prior art provides any evidence that inhibition of SEQ ID NO:3 leads to treatment of any eye disorder such as retinitis pigmentosa. Prior or post-filing art showing or suggesting that inhibition of SEQ ID NO:3 or its protein product by any means---small molecule, antibody, antisense, or dsRNA---produces a therapeutically relevant effect would be remedial to overcoming this portion of the rejection. Currently, the examiner finds no such evidence and the mere assertion in light of the evidence linking many factors to eye disease represents a hoped-for function and a starting point for future research, but does provide the type of direction, guidance, and assurance needed to enable the method under 35 USC 112, first paragraph.

Given the complexity of the biochemistry of such disorders and the many genes expressed in the eye which may or may not be directly related to the disorders, one of skill would require specific guidance as to how to design the dsRNAs effective for inhibiting the expression of a gene involved in any disorder in order to treat the disorder. Such comprehensive disclosure is lacking.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by

the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Response to Arguments

The reply filed on 11/16/07 and 2/7/08 is not fully responsive to the prior Office Action because the reply does not particularly point out any supposed errors in the rejection for lack of enablement. See 37 CFR 1.111. Applicant replied to the written description rejection, but not the enablement rejection.

Claim Rejections - 35 USC § 102---maintained

Claims 1, 4-6, 9, 10, 16, 19 remain rejected and new claims 96 and 98 are rejected under 35 U.S.C. 102(e) as being anticipated by King et al. (US 2002/0165158 A1).

King et al. taught methods for making and using siRNA targeted to PKCβ to treat angiogenesis-related disorders, including diabetic retinopathy and other neovascular disorders of the eye (page 1, 8, 10, and 11, for example). It is taught that the agent [the PKCβ antagonist] may be administered to the eye, e.g., as aqueous eye drops or in a cream, lotion or other vehicle suitable for administration onto the eye surface (paragraph 125, page 10), systemically, or transmucosally (paragraph 190). Additionally, it is said that the pharmaceutical composition may be administered directly into a retinal tissue, arthritic tissue, or tumor tissue of the subject (paragraph 194). Several types and forms of compositions are described (page 10).

With regard to new claim 96, at paragraphs 215-240, King et al. taught methods for detecting and monitoring the expression of the target gene and protein product thereof using a variety of protein and gene expression assays.

Accordingly, King et al. anticipate the instant claims.

Response to Arguments

Applicant argues King et al. does not exemplify the use of dsRNA or document operability of any dsRNA to treat an eye disorder. Applicant states King et al. does not mention the blood-retina barrier or mention options for overcoming the blood retina barrier.

Applicant's arguments have been fully considered but are not persuasive. Applicant appears to be arguing King et al. is not enabling for a method of treating a disorder of the eye or even for a method of delivering an siRNA into the eye from outside the blood retina barrier.

However, King et al. describe each and every limitation of the instantly claimed method in as much detail as recited in the instant claims. The claims neither expressly recite nor require any condition, feature, or step not disclosed by King et al. While applicant may have verified that systemic administration of an siRNA may be used to effectively inhibit the expression of a gene in the eye, King et al. recommends doing exactly that, using the same material and according to the same steps recited by the claim. King et al. recommends administration of the agent outside the blood retina barrier via systemic or topical application. Mention of the blood retina barrier is not germane nor necessary, because at least one of the recommended routes of delivery is outside the blood retina barrier. It is not necessary for the rejection that King et al. recognize or teach that fact. Furthermore, there is no requirement for anticipation of a claim that the prior art

provide a working example of what applicant is claiming. The prior art is relevant for all that it discloses, explicitly, implicitly, and inherently.

MPEP 2121.01 states that a reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). It is the position of the Examiner that King et al. enables one of skill to make and use the siRNA disclosed therein in the manner intended to administer the siRNA systemically or topically, directly to the eye. The instant claims as now written are indistinguishable from this method, and the fact that Applicant has verified that these routes of administration do in fact result in delivery of siRNA into the eye does not by itself render the claim patentatable because applicant has simply confirmed the operability of what was taught and/or suggested by the prior art.

Applicant is reminded that there is nothing in the instant claims to distinguish the method over that taught by King et al. While applicant generally alleges King et al. does not enable a method within the scope of that now claimed, the methods are indistinguishable, and Applicant does not point to any feature(s) or condition in the claims not taught by King et al. Because King et al. provide the material and methods to make and use dsRNA against at least one gene to treat at least one disorder of the eye, the public was in possession of the method disclosed therein, which is identical in every aspect with that now claimed. If it is applicant's position the instant claims are distinct from the method disclosed by King et al., Applicant should cite that or those feature(s) and/or amend the claims to include that or those feature(s), which, if essential to the

operability of the instant methods, must, in any event, be recited in the claims for the claims to be enabled (MPEP 2164.08(c) and 2172.01). Currently, there is no evidence to suggest the claims lack any essential elements (MPEP 2164.08(c)), and King et al. teaches each of the elements and steps recited in the instant claims.

Claim Rejections - 35 USC § 103---maintained

Claims 1, 4-6, 9, 10, 16, and 19 remain rejected and new claims 96 and 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al. (US Patent 5,814,620); Dryja et al. (US Patent 5,498,521), Weber et al. (1991) *Nucleic Acids Res.* 19:6263-6268; Epstein (1998) *Methods: A Companion to Methods in Enzymology* 14:21-33; Collins et al. (1992) "The human beta-subunit of rod photoreceptor cGMP phosphodiesterase: complete retinal cDNA sequence and evidence for expression in brain" *Genomics* 13 (3): 698-704; and Tuschl et al. (US Patent Application 2004/0259247 A1); Bass (2001) *Nature* 411:428-9.

With regard to new claim 96, Dryja et al. teach antisense probes that may be used to diagnose the presence and relative quantity of the beta subunit of rod retinal cGMP phosphodiesterase.

With regard to new claim 98, Robinson et al. taught systemic delivery of antisense oligonucleotides for inhibition of a gene such as VEGF in the eye.

Robinson et al. taught a method for treating diabetic retinopathy and macular degeneration comprising the step of administering to a subject afflicted with diabetic retinopathy a therapeutic amount of an antisense oligonucleotide specific for vascular endothelial growth factor nucleic acid and effective in inhibiting the expression of vascular endothelial growth

factor in the retina, including choroidal neovascularization (claim 1 and Examples 4 and 5, column 15, for example). Several representative embodiments of anti-VEGF oligonucleotides are disclosed at Table 1, column 6). The antisense oligonucleotide may be composed of ribonucleotides, deoxyribonucleotides, or a combination thereof (column 7, lines 30-35; claim 5). They may be combined with a variety of pharmaceutically acceptable carriers and formulated in pyrogen-free compositions in a way suitable for intraocular, intravitreal, or systemic administration (column 10, lines 20-40; column 11, lines 5-15). It is said the antisense oligonucleotide may be formulated as a sterile, buffered, isotonic solution (column 10, lines 20-35).

Robinson et al. further teach methods for delivering antisense oligonucleotides intraocularly to cells in the eye to treat diseases associated with the eye. Robinson et al. teach specifically methods for targeting VEGF in retinal cells using several forms of administration. For example, Robinson et al. taught that "Intravitreal injections of oligonucleotides against VEGF can be an effective means of inhibiting retinal neovascularization in an acute situation. However for long term therapy over a period of years, systemic delivery (intraperitoneal, intramuscular, subcutaneous, intravenous) either with carriers such as saline, slow release polymers, or liposomes should be considered" (column 11). Similarly at columns 9 and 10, Robinson et al. taught that the synthetic oligonucleotide could be administered by intraocular, oral ingestion, inhalation, or cutaneous, subcutaneous, intramuscular, or intravenous injection. Thus, Robinson taught systemic administration, which is considered to be outside the blood-retina barrier, as evidenced by claim 22 (now cancelled).

While Robinson et al. taught methods and materials making and using antisense oligonucleotides to treat eye diseases, including those recited in the claims, Robinson et al. do not teach dsRNAs or siRNAs for modulating genes associated with eye disease or antisense or dsRNAs specifically targeted SEQ ID NO:3.

Nevertheless, SEQ ID NO:3 is shown in the prior art, and its correlation to eye disorders is well established.

With regard SEQ ID NO:3, the instant application teaches that SEQ ID NO:3 corresponds to the beta-subunit of rod cGMP phosphodiesterase corresponding to GenBank Accession No. NM_000283 (page 18), which is 3283 nucleotides in length. A standard search of SEQ ID NO:3 finds that SEQ ID NO:3 corresponds to GenBank Accession No. S41458, which is 3231 nucleotides in length (see search result in Exhibit A, provided with the Action of 7-12-06). A comparison of NM_000283 and S41458 shows that NM_000283 comprises S41458 (compare Exhibits B and C, provided with the Action of 7-12-06).

Weber et al. teach the full length sequence of rod cGMP phosphodiesterase corresponding to GenBank Accession No. NM_000283 (See Exhibit C, provided with Action of 7-12-06). Weber et al. also expressly taught a link between cGMP phosphodiesterase and retinal degeneration in the rd mouse, and states that any one of the many genes involved in the complex biochemistry of the eye could theoretically impair vision, and that few forms of human hereditary retinal degeneration such as gyrate atrophy of the choroid and retina, choroideraemia, and autosomal dominant retinitis pigmentosa have been linked to mutations in specific genes (page 6264).

Dryja et al. teach methods diagnosing in a mammal, e.g., a human subject, an increased likelihood of, inclination toward, or susceptibility to developing a disease, e.g., retinitis pigmentosa, in which a mutant form of a human photoreceptor protein is a causative agent. Human photoreceptor proteins said to be potential causative agents include the beta subunit of rod retinal cGMP phosphodiesterase (column 2, top). Dryja et al. teach that mutant photoreceptor proteins such as cGMP phosphodiesterase may be involved in hereditary retinal degenerative diseases in which progressive, bilateral degeneration of retinal structures leads to loss of retinal function; these diseases include, for example, age-related macular degeneration (column 1).

In an exemplary embodiment, Dryja et al. teach antisense probes that may be used to diagnose the presence and relative quantity of the beta subunit of rod retinal cGMP phosphodiesterase corresponding to the gene disclosed by Weber et al. (see Example 9, column 15, lines 35-45), which, as explained above, also corresponds to SEQ ID NO:3. It was found that patients with mutations in the PDE .beta. gene had clinical findings typical of retinitis pigmentosa (column 17, top). Accordingly, Dryja et al. suggest that the expression of a mutant form of the protein encoded by SEQ ID NO:3 is associated with a disorder of the eye.

Epstein et al. teach the use of antisense inhibitors for specifically regulating phosphodiesterase genes, both *in vitro* and *in vivo*. It is taught for example that the goal of antisense technology is to develop small oligonucleotides, plasmids, or retroviral vectors that can be introduced into cells in order to inhibit gene products specifically. Epstein et al. teach that antisense oligos can be used to inhibit essentially any isoform of PDE (page 21). Epstein et al. provide a complete blueprint for the design and preparation of antisense oligonucleotides against the known PDE gene sequences (see pages 22-25). Epstein et al. state that a number of excellent

reviews have been written recently that describe the characteristics of the different PDE isoforms, their regulation, function, and progress in development of pharmacological inhibitors of PDE as therapeutic agents (page 21, 2nd column). Epstein et al. cite a number of additional references as support therein.

Collins et al. echos and reinforces the disclosures of Dryja et al. and Epstein et al., teaching the full length cDNA sequence of rod cGMP phosphodiesterase, which is found to be 100% identical to instant SEQ ID NO:3, now recited in claim 19. Collins et al. state that the molecular cloning of the cDNA encoding for the PDEB represents the first step in establishing whether this gene plays a causative role in any one of the several human hereditary retinopathies.

Tuschl et al. teach short double-stranded RNA molecules for mediating target-specific gene silencing via RNA interference (RNAi) in human cells (paragraphs 10, for example). It is taught that double-stranded RNA molecules 19-25 nucleotides in length have RNAi activity and may trigger the specific degradation of homologous RNAs within the region of identity with the dsRNA (paragraphs 5, 7, 11, and 17 for example). Tuschl et al. teach that siRNA duplexes are preferably composed of 21-nt antisense siRNAs and should be selected to form a 19-bp double helix with 2-nt 3' overhanging ends (paragraphs 9, 11, 179).

In summary, the Tuschl et al. reference is considered to be a complete blueprint for the design, synthesis, and use of short interfering, double-stranded RNA, in modified or unmodified forms, against any desired target gene. The reference contains detailed descriptions and several examples typifying the use of siRNA in cell culture, and the Application Publication expressly suggests the use of siRNA *in vivo* for use in therapeutic and clinical settings (paragraphs 31-36).

Importantly, Tuschl et al. also compare siRNA methodology to that of antisense and ribozyme techniques for inhibiting gene expression. At paragraph 148, for example, Tuschl et al. state that siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments. At paragraph 137, Tusch et al. state that the remarkable finding that synthetic 21 and 22 nt siRNA duplexes can be used for efficient mRNA degradation provides new tools for sequence-specific regulation of gene expression in functional genomics as well as biomedical studies. The siRNAs may be effective in mammalian systems where long dsRNAs cannot be used due to the activation of the PKR response. As such, the siRNA duplexes represent a new alternative to antisense or ribozyme therapeutics.

Bass teaches that, like some antisense oligonucleotides, which trigger RNase H-catalyzed cleavage of their targets, siRNAs trigger the degradation of complementary messenger RNAs (page 428 and Fig. 1). A general outline of the RNAi mechanism is taught, showing how siRNA-mediated RNAi may be used to interfere with gene expression using siRNAs directed against specific mRNA sequences (Fig. 1). Bass teaches that RNAi has repeatedly proven itself to be more robust that antisense techniques: it works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely. Furthermore, siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments.

Thus, the prior art teaches, in general, that siRNAs and antisense oligonucleotides can be used to produce the same effect, albeit with different potencies and by different biochemical

mechanisms. siRNAs and antisense oligos can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids may be used to prevent the expression of a gene in a cell. For example, Bass teaches that antisense RNA is another technique to prevent the expression of particular genes (page 429). Thus, in this sense, siRNAs and antisense oligos are art-recognized equivalents that may be used for the same purpose: reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.)

Nevertheless, as explained above, siRNAs possess certain advantages over antisense oligos, which would motivate one of ordinary skill in the art to select siRNAs over antisense oligos to more efficiently block and/or reduce the expression of any given target gene, particularly a gene known to be involved in cancer.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to make and use siRNAs, as taught by Tuschl et al. and Bass, targeted to VEGF mRNA and SEQ ID NO:3, corresponding to beta subunit of rod cGMP phosphodiesterase, to inhibit the expression of VEGF and mutant isoforms of SEQ ID NO:3 and consequent development of ocular diseases associated with the expression of VEGF and mutant isoforms of SEQ ID NO:3, as taught by Robinson et al. Weber et al., and Dryga et al. Further, it would have been obvious to administer said siRNAs by any number of means including systemically, as taught by Robinson et al. It would further have been obvious to apply the siRNAs directly to the area affected by the disease—the eye—by direct application, injection, or topically, as by eye drops. There is nothing in the art nor any evidence of record showing any express teaching away from the use of eye drops for the administration of any oligonucleotide-

based therapeutic. It is a matter of common sense to apply the therapeutic agent directly to the area of treatment.

One would have been both well motivated and have had a reasonable expectation of success given that Dryja et al. teach that mutant isoforms of beta phosphodiesterase (i.e., SEQ ID NO:3) may predispose individuals to macular degeneration, and given that Robinson et al. teach that antisense compounds may be used effectively in retinal cells specifically to inhibit the expression of genes associated with macular degeneration, and given that Epstein teaches that antisense compounds may be used effectively to inhibit the expression of phosphodiesterases in particular. Given that Tuschl et al. and Bass teach that siRNAs are in general more potent than antisense oligonucleotides for reducing gene expression in cells, one of skill would have been motivated to substitute siRNAs for antisense oligonucleotides in the methods of Dryja et al. and/or Epstein et al. to silence the expression of genes such as SEQ ID NO:3 associated with eye disorders.

One would have had a reasonable expectation of success in targeting mutant forms of SEQ ID NO:3 as well as SEQ ID NO:3 itself given that Dryja et al. together with Collins et al. teach both the wild type form, as disclosed in Weber et al., and common mutations thereof leading to eye-related disease (see example 9).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 11/16/07 and 2/7/08 traversing the instant rejection under 35 USC 103 have been fully considered but are not persuasive.

Applicants argues the cited references do not teach administration of antisense or dsRNA outside the blood-retina barrier. As explained in the previous Action, contrary to Applicant's position, the cited references as a whole clearly taught and/or suggest that therapeutic oligonucleotides such as antisense and siRNA may delivered into cells in the eye by a number of different routes of delivery, including systemic. While Applicant contends the prior art cited herein is not relevant because it does not explicitly exemplify systemic delivery of dsRNA, the the prior art does not need to exemplify or even characterize applicant's claimed invention as a preferred route to anticipate or render obvious applicant's claimed invention.

While Applicant may have shown that siRNAs may be delivered into the eyes by systemic delivery, the prior art reasonably suggests using systemic delivery to deliver antisense oligonucleotides into the eye, as evidenced by at least Robinson et al. Again, as in the rejection over King et al. above under 35 USC 102, there is no element or step in the claim to distinguish the instant invention over those methods disclosed and/or reasonably suggested by the prior art.

"[T]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). MPEP 2141.02

Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. MPEP 2123.

For these same reasons, and given that the use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned---they are part of the literature of the art, relevant for all they contain---one of skill would have been motivated to try a number of different delivery methods including systemic and topical delivery. Given that the prior art taught several modes of administration of antisense oligos for treating eye disease, and that eye disease caused by abnormal gene expression was amenable to in vivo delivery of antisense oligos, and given that Tuschl et al. and Bass both encouraged the use of siRNAs in mammals for both in vitro studies and in vivo therapy, motivation is clear. There is absolutely no evidence to suggest one of skill would be discouraged from using siRNA to treat eye disease.

The fact that the prior art did not appreciate or recognize that dsRNA readily passed through the blood-retina barrier is of no consequence, absent evidence that one of skill would have been expressly discouraged from administering antisense or dsRNA outside the blood retina barrier for the treatment of eye disease. See MPEP 2112.

Applicants will note that the rationale for combining the cited prior art teachings does not rely on the recognition of the undisclosed property of crossing the blood-retina barrier without the need for delivery enhancing vehicles, but on the fact that the prior art taught that eye disorders may be treated by administering antisense, and that siRNAs are functionally equivalent to but much more potent than antisense oligos. There is reason to suggest one of skill would be motivated to use siRNAs in place of antisense in the methods of Robinson et al. for example.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LW
Examiner AU1635
July 9, 2008

/Sean R McGarry/
Primary Examiner, Art Unit 1635